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(54) THERAPEUTIC AGENT FOR DIABETIC KERATOPATHY

(57)Abstract:

PURPOSE: To obtain a therapeutic agent for diabetic keratopathy, containing an imidazoline derivative as an active ingredient and having the form of a peroral agent or an eye drop.

CONSTITUTION: This therapeutic agent for diabetic keratopathy contains (2S,4 S)-6-fluoro-2',5'-dioxospiro[chroman-4,4'-imidazoline]-2-carboxamide as an active ingredient. The agent can be prepared as a dosage form such as a peroral pharmaceutical preparation such as a tablet, a capsule, a powder or a granule and a parenteral pharmaceutical preparation such as an eye drop, a parenteral injection or a suppository. The dose thereof is 0.01-1% eye drop applied to the eyes in one to several divided portions in the case of the eye drop. The daily dose for an adult is 0.125-100mg, preferably 0.5-2mg administered in one to several divided portions in the case of the oral pharmaceutical preparation. The agent is effective for diabetic corneal epitheliosis, imperception and endotheliosis.

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CLAIMS

[Claim(s)]
[Claim 1] 2S, (4S)-6-fluoro - 2', 5' - Dioxo SUPIRO [chroman -4 and 4'-imidazoline]-2 - Diabetic keratopathy therapy agent which makes the carboxamide an active principle.
[Claim 2] The diabetic keratopathy therapy agent according to claim 1 which has the gestalt of an oral agent, ophthalmic solutions, etc., and is used for the diabetic cornea epitheliosis, diabetic cornea **********, and the diabetic cornea endotheliosis.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention is 2S and (4S)-6-fluoro. - They are 2' and 5'. - Dioxo SUPIRO [chroman -4 and 4'-imidazoline]-2 - The diabetic keratopathy therapy agent which makes the carboxamide an active principle is started, it has an ophthalmic-solutions gestalt especially and the constituent used for the diabetic cornea epitheliosis, the diabetic cornea imperception, and the diabetic cornea endotheliosis is started.
[0002]
[Description of the Prior Art] 2S, (4S)-6-fluoro - 2', 5' - Dioxo SUPIRO [chroman -4 and 4'-imidazoline]-2 - It is the compound discovered by this people firm, the operation over a diabetic neuropathy, an antiulcer action, and the drugs for circulatory organs are accepted, and since the operating safety over a long period of time is high, the carboxamide is during the clinical trial as drugs for current taking orally. [EP-B -264586, U.S.4,985,573 (Japanese Patent Publication No. No. 72227 [three to]), U.S.5,155,125 (publication number 3-215435 number), U.S.5,164,391 [0003] (publication number 3-106885 number), etc.
[Problem(s) to be Solved by the Invention] A diabetes-mellitus karatopathy is a disease various abnormalities are accepted to be to the epithelium anterius corneae, consciousness (Schwann cell), and an endothelial cell. When collapse of a cornea is critical, it is often intractable for a bubble karatopathy to occur and to carry out the failure of the visual function remarkably etc. However, a remedy that the developmental mechanism is not yet clear and effective is not found out, either.
[0004] By the way, although a cornea endothelial cell has an important function, even if there is no ability to regenerate or there is, it is very scarce. However, in a diabetic, it will remain for ten years, and may come out of the onset, the symptoms of a simple diabetic retinopathy may be shown, and it may result in a growth retinopathy, amotio retinae, and loss of eyesight soon. In order to prevent the progress, a cornea endothelial cell is easily affected by strong stress, such as an intraocular implant permutation way to application of the photocoagulation, vitreous surgery, etc., or a cataract, and it is supposed that a karatopathy will be caused.
[0005] Although the brittleness in a diabetic's cornea does not result in a karatopathy, if it observes a diabetic's endothelial cell by speculative microscope, malformation, such as a size different and deformation, is accepted and existence of a diabetic endothelium-camerae-anterioris failure is already suggested.
[0006] Although there is no report with the clear number of patients of a diabetes-mellitus karatopathy, for Kitasato University ophthalmology Shimizu and others, a retinopathy patient's rate of cornea damage is 56% and 17% of normal persons. It is overwhelmingly high, and cornea tissue compared with the normal person and has reported having brittleness. Now, a diabetic is on a potential target. 6 million people are counted, it is predicted that it continues to increase increasingly, and an appearance of effective drugs is strongly desired from causing serious problems, such as spoiling the increase and QOL of a health care cost to this disease.
[0007]
[Means and Methods for Solving the Problem] This invention is 2S and (4S)-6-fluoro. - They are 2' and 5'. - Dioxo SUPIRO [chroman -4 and 4'-imidazoline]-2 - The carboxamide finds out that it is effective in making diabetic keratopathy without an effective cure improve, and offers a patient's health care cost, welfare, and drugs very useful in respect of QOL (QOULITY OF LIFE).
[0008] The pharmaceutical preparation form of the therapy agent to the diabetic keratopathy of this invention can be used as oral pharmaceutical preparation, such as a tablet, a capsule, powder, and a granule, or parenteral pharmaceutical preparation, such as ophthalmic solutions, injections, and suppositories, using the usual pharmaceutical preparation technique. A dose is [as opposed to / the case of taking orally / again / an adult] per day by usually applying [0.01%] eyewash in 1 time or several steps in ophthalmic solutions -

1% in the case of ophthalmic solutions, although it changes with a symptom, age, the prescribing [for the patient]-a medicine method, pharmaceutical forms, etc. 0.125-100mg The purpose can be attained within the limits by prescribing 0.5-2mg for the patient in 1 time or several steps preferably. An example is raised to below and this invention is further explained to a detail.
[0009]
[Example]
Example [of a drug effect pharmacological test] 1 test method: The experiment was conducted according to Akagi's and others approach (Japanese ophthalmology bulletins 37, 809, and 1986). The Sprauge Dawley system rat (one groups [15]) with a weight of 50g (3 weeks old of after the birth) was used, and it divided into the following three groups. (1) In a control group, it is a usual diet breeding group for research (normal control drug), and (2). 50% galactose content diet breeding group (galactose independent group) and (3) They are 2S and (4S)-6-fluoro to 50% galactose content diet. - 2', 5' - Dioxo SUPIRO [chroman -4 and 4'-imidazoline]-2 - Group which carried out 3 mg/kg forcible internal use of the carboxamide (it abbreviates to compound A below) (compound A galactose group). The rat of each group was bred for about six weeks. Freeze fracturing of a cornea endothelial cell is the point diameter beforehand cooled at -70 degrees C with acetone dry ice to the cornea center section of each group. The 1.5mm stainless steel rod was hit for 20 seconds, it passed through it, and freeze fracturing of the endothelial cell was carried out in cornea. The cornea was extracted by Nembutal fatal anesthesia with time after freeze fracturing, and it observed by the following approaches.
[0010] Light-microscope-observation: 0.1M phosphate buffer solution which contains glutaraldehyde for a cornea 1% paraformaldehyde and 1% (pH7.4) After immobilization and the re-immobilization by 1% osmium tetroxide, alcoholic dehydration was carried out and embedding was carried out to Epon resin by the predetermined approach. The light microscope intercept was observed after the toluidine purple-blue color dyeing color.
[0011] Expansion sample observation: It was immersed in 60mM and 2Na EDTA buffer solution with un-fixing a cornea, and it exfoliated from the posterior limiting layer and only the endothelial cell layer after methanol fixation was appended to slide glass. The sample was dyed toluidin blue and observed in the light microscope.
[0012] result: -- after [freeze fracturing] five-day: -- a normal control group -- a freezing part -- the hill of 2-3 layers -- the ** multistory field was seen and the endothelial cell was restored in light microscope. On the other hand, by the galactose independent group, two or more structures of a large-sized circular bulge were seen in accordance with the freezing part. The denaturation cell population existed in the interior of a bulge. The magnitude was small although the bulge structure was sometimes seen also by the compound A galactose group. Moreover, the part where the countless nucleus crowds also with the expansion sample in the cornea center section was seen.
[0013] After [freeze fracturing] seven days: The part stratified by the normal control group and the compound A galactose group at this stage was not seen, and flattening was carried out completely and it normalized. As for the bulge structure, as for the galactose independent group, this stage also remained in the example more than a moiety. It is the thing of long and slender cytoplasm, and was constituted rather than it reduced multistory height and the endothelial cell was also circular compared with the image seen on the 5th. The expansion sample image also reached far and wide, and nuclear high density and multistory part were seen.
[0014] The clear usefulness of this invention was observed based on the result of the example 1 of an example of drug effect pharmacological test 2 drug-effect pharmacological test. The approach of an experiment was enforced according to the example 1, and extracted the cornea on the 5th after freeze fracturing of (1) normal control group, (2) galactose independent group, and (3) compound-A galactose group. Paraffin embedding of the cornea of the left eye of a rat was carried out by the predetermined approach, the hematoxylin and eosin stain was performed after thin sectioning, and light microscope observation was performed.
[0015] Result: The multistory part and the upheaval structure of a cornea endothelial cell of a light microscope observation freezing part were made into the restoration process of a cornea endothelial cell failure, and were accepted in 25% of eyeball by the normal control group on the 5th after freeze fracturing. On the other hand, it accepted to 100% of all eyeballs, and the difference is significant ($P< 0.05$) statistically, and restoration of a cornea endothelial cell failure was delayed by the galactose independent group. on the other hand, by the compound A galactose group, the multistory part and the upheaval structure of a cornea endothelial cell are accepted in 22% of eyeball -- having -- a galactose independent group -- comparing -- statistical -- being significant ($P< 0.01$) -- it normalized. Also statistically, that administration

of compound A makes cornea endothelial cell failure restoration delay of this model improve became whether to be **.
[0016] The result of the example 2 of a trial (Table 1)
Effectiveness over restoration delay of the freeze-fracturing cornea endothelial cell of a galactosemia rat [the observation result on the 5th after freeze fracturing]
[0017]
[Table 1]
Treatment The number of observation corneas The number of failure restoration delay corneas (%)
(1) Normal control group 8 2 (25)
(2) Galactose independent group 8 8 (100)
(3) Compound A galactose group 9 2 (22)
[0018] Compound A administration was made to improve to cornea endothelial cell failure restoration delay of the galactosemia rat which is the diabetic simplest animal model as mentioned above, and treating diabetic keratopathy also clinically was suggested strongly.
[0019] Compound A, such as an example of pharmaceutical preparation; (2S, 4S) -6-fluoro - 2', 5' - Dioxo SUPIRO [chroman -4 and 4'-imidazoline]-2 - Carboxamide [0020] Compound A in example of pharmaceutical preparation 1 formula A100ml 0.10g phosphoric-acid 1 hydrogen sodium 0.76g sodium dihydrogenphosphate 0.16g sodium chloride 0.42g benzalkonium chloride 0.01g sterile purified water ** Amount [0021] Compound A is added, after adding a sodium dihydrogenphosphate, phosphoric-acid 1 hydrogen sodium, and a benzalkonium chloride to 80ml of process sterile purified water and dissolving in it. After dissolving compound A, sterile purified water is added and it is 100ml about the whole quantity. It carries out and ophthalmic solutions are presented.
[0022] Compound A in formula B100ml 0.10g phosphoric-acid 1 hydrogen sodium 0.76g sodium dihydrogenphosphate 0.16g sodium chloride 0.40g benzalkonium chloride 0.01g cane sugar 0.05g sterile purified water ** Amount [0023] Ophthalmic solutions were **(ed) by the same approach as the process formula A.
[0024] 0.4g of charge regulators shown in Table 2 of the example of pharmaceutical preparation 2 following, and purification yolk lecithin 1.6 g After carrying out the mixed dissolution of the 8.0g of the oily components shown in the following table 3 in chloroform / 50ml of methanol (5/1 and V/V) mixtures, 0.1-1.0g is added for compound A, and a solvent is removed completely. It is 90g of sterile purified water to this. It adds, high-pressure (1500kg/cm 2) emulsification is carried out by micro sieve TAIZA, and it considers as lipid microsphere 10% (W/W).
[0025] Lipid microsphere in 100ml of formulas 50.0g phosphoric-acid 1 hydrogen sodium 0.76g sodium dihydrogenphosphate 0.16g sodium chloride 0.40g benzalkonium chloride 0.01g cane sugar 0.05g sterile purified water ** Amount [0026] Ophthalmic solutions were **(ed) by the same approach as the process formula A.
[0027]
[Table 2]
** Load Tone ** Agent Dimyristoyl phosphatidylglycerol dimyristoyl phosphatidic acid phosphatidylinositol phosphatidylserine oleic acid capric-acid sodium [0028]
[Table 3]
Oil Sex ** Part Size Beans Oil medium-chain-fatty-acid triglyceride tocopherol acetate squalane [0029] The

処方

化合物A	2㎎
ショ糖	25㎎
結晶セルロース	30㎎
乳糖	適　量
	180㎎

example 3 of pharmaceutical preparation

[0030] Process compound A and cane sugar are kneaded with ethanol/water (1/1, W/W), crystalline cellulose and a lactose are added after desiccation, the lubricant with which pharmaceutical preparation is usually presented is added, and it considers as oral pharmaceutical preparation, such as a tablet, a capsule, and a granule, with a conventional method.

処方

化合物A	1mg
ショ糖	10mg
結晶セルロース	30mg
乳糖	適 量
	180mg

[0031] The example 4 of pharmaceutical preparation

[0032] Oral pharmaceutical preparation was **(ed) by the same approach as the example 3 of process pharmaceutical preparation.

[0033]

[Effect of the Invention] Although a remedy that the developmental mechanism of a diabetes-mellitus karatopathy is not yet clear and effective is not found out, either, it is the disease various abnormalities are accepted to be to the epithelium anterius corneae, consciousness (Schwann cell), and an endothelial cell, and when collapse of a cornea is critical, it is often intractable for a bubble karatopathy to occur and to carry out the failure of the visual function remarkably etc. This invention is 2S and (4S)-6-fluoro. - They are 2' and 5'. - Dioxo SUPIRO [chroman -4 and 4'-imidazoline]-2 - It is the diabetic keratopathy therapy agent which makes the carboxamide an active principle, and it has taking orally and an ophthalmic-solutions gestalt especially, and has effectiveness in the diabetic cornea epitheliosis, the diabetic cornea imperception, and the diabetic cornea endotheliosis.

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最終頁に続く

(54)【発明の名称】　糖尿病性角膜症の治療剤

(57)【要約】
【目的】糖尿病角膜症はその発生機序は未だ明らかではなく、角膜上皮、知覚（シュワン細胞）および内皮細胞に種々の異常が認められる疾患であり、角膜の崩壊が重篤な場合、水泡性角膜症が発生し視機能を著しく障害する等しばしば難治性であり、有効な治療薬は未だ見い出されていない。本発明はこの有効な治療薬を提供する。
【構成】(2Ｓ,4Ｓ)-6-フルオロ-2',5'- ジオキソスピロ［クロマン-4,4'-イミダゾリン］-2- カルボキサミドを有効成分としており、経口、点眼剤投与形態を有し、糖尿病性角膜上皮症、糖尿病性角膜知覚低下、糖尿病性角膜内皮症に使用される。

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【特許請求の範囲】

【請求項１】(2Ｓ,4Ｓ)-6-フルオロ-2',5'- ジオキソスピロ［クロマン-4,4'-イミダゾリン］-2- カルボキサミドを有効成分とする糖尿病性角膜症治療剤。

【請求項２】経口剤及び点眼剤等の形態を有し、糖尿病性角膜上皮症，糖尿病性角膜知覚低下症、糖尿病性角膜内皮症に使用される請求項１記載の糖尿病性角膜症治療剤。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は(2Ｓ,4Ｓ)-6-フルオロ-2',5'- ジオキソスピロ［クロマン-4,4'-イミダゾリン］-2- カルボキサミドを有効成分とする糖尿病性角膜症治療剤に係り、殊に点眼剤形態を有し、糖尿病性角膜上皮症、糖尿病性角膜知覚低下、糖尿病性角膜内皮症に使用される組成物に係る。

【０００２】

【従来の技術】(2Ｓ,4Ｓ)-6-フルオロ-2',5'- ジオキソスピロ［クロマン-4,4'-イミダゾリン］-2- カルボキサミドは本出願人会社によって発見された化合物であり、糖尿病性神経障害に対する作用、抗潰瘍作用、循環器官用薬剤が認められ、長期間にわたる使用安全性が高い事から現在経口用医薬品としての臨床試験中にある。［EP-B-264586 、U.S.4,985,573(特公平 3-72227号）、U.S.5,155,125(特開平 3-215435 号）、U.S.5,164,391(特開平 3-106885 号）等

【０００３】

【発明が解決しようとする課題】糖尿病角膜症は角膜上皮、知覚（シュワン細胞）および内皮細胞に種々の異常が認められる疾患である。角膜の崩壊が重篤な場合，水泡性角膜症が発生し視機能を著しく障害する等、しばしば難治性である。しかしながら、その発生機序は未だ明らかではなく有効な治療薬も見い出されていない。

【０００４】ところで、角膜内皮細胞は重要な機能を有するにもかかわらず再生能力はないか、あってもきわめて乏しい。しかし、糖尿病患者では発症から10年余りで単純糖尿病網膜症を発症し、やがて増殖網膜症、網膜剥離、失明に至ることがある。その進展を防止するため光凝固術、硝子体手術等の適用、あるいは白内障に対する眼内レンズ置換術などの強いストレスにより容易に角膜内皮細胞に影響を与え、角膜症を引き起こすとされている。

【０００５】糖尿病患者の角膜における脆弱性は、角膜症に至らないまでも糖尿病患者の内皮細胞をspeculative microscopeによって観察すると、大小不同，変形などの形態異常を認め，糖尿病性角膜内皮障害の存在が既に示唆されている。

【０００６】糖尿病角膜症の患者数は明確な報告はないが、北里大眼科清水らは網膜症患者の角膜損傷率は56%、正常者17% と圧倒的に高く、角膜組織は正常者に比し脆弱性を有すると報告している。糖尿病患者は今や潜在的に 600万人を数え、今後も益々増加すると予測されており、本疾患に対する医療費の増大やＱＯＬを損なう等、深刻な問題を引き起こすことから、有効な薬剤の登場が強く望まれている。

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【０００７】

【課題を解決するための手段及び方法】本発明は、(2Ｓ,4Ｓ)-6-フルオロ-2',5'- ジオキソスピロ［クロマン-4,4'-イミダゾリン］-2- カルボキサミドが、有効な治療法がない糖尿病性角膜症を改善させるのに有効であることを見出だしたものであり、患者の医療費、福祉、QOL(QOULITY OF LIFE)の面で非常に有用な薬剤を提供する。

【０００８】本発明の糖尿病性角膜症に対する治療剤の製剤形は、通常の製剤技術を用いて、例えば錠剤、カプセル剤、散剤、顆粒剤等の経口製剤として、あるいは点眼剤、注射剤、坐剤等の非経口製剤として使用できる。投与量は、症状、年齢、投与法、剤型等により異なるが、通常は点眼剤の場合0.01% ～1%点眼剤を１回または数回に分けて点眼することにより、また経口の場合、成人に対して、一日当たり 0.125～100mg の範囲内、好ましくは0.5 ～２mgを１回または数回に分けて投与することにより目的を達成することができる。以下には、実施例をあげ本発明を更に詳細に説明する。

【０００９】

【実施例】

薬効薬理試験例１

試験方法：実験は赤木らの方法（日本眼科紀要37,809,1986)に準じ実施した。体重50ｇ（生後３週齢）のSprague Dawley系ラット（１群15匹）を使用し、以下の３群に分けた。(1) 対照群には研究用通常食餌飼育群（正常対照薬）、(2) 50%ガラクトース含有食餌飼育群（ガラクトース単独群）、(3) 50%ガラクトース含有食餌に(2Ｓ,4Ｓ)-6-フルオロ-2',5'- ジオキソスピロ［クロマン-4,4'-イミダゾリン］-2- カルボキサミド（以下化合物Ａと略す）を３mg/kg強制経口投与した群（化合物Ａガラクトース群）。各群のラットを約６週間飼育した。角膜内皮細胞の凍結破壊は各群の角膜中央部にあらかじめアセトン・ドライアイスで－70℃に冷却した先端部直径 1.5mmのステンレス棒を20秒間あて経角膜的に内皮細胞を凍結破壊した。凍結破壊後経時的にネンブタール致死麻酔にて角膜を摘出し以下の方法で観察した。

【００１０】光顕的観察：角膜を１%パラホルムアルデヒド・１%グルタルアルデヒドを含む0.1Mリン酸緩衝液(pH7.4）固定と１%四酸化オスミウムによる再固定後、アルコール脱水し，所定の方法にてエポン樹脂に包埋した。光顕切片はトルイジン青紫色染色後観察した。

【００１１】伸展標本観察：角膜を未固定のまま60mM・2Na EDTA緩衝液に浸漬し，メタノール固定後内皮細胞層のみをデスメ膜から剥離しスライドガラスに添附した。

試料はトルイジン青に染色し光顕にて観察した。

【００１２】結果：

凍結破壊後５日：正常対照群では凍結部位に２～３層の丘状重層領域がみられ、内皮細胞は光顕的に修復されていた。一方，ガラクトース単独群では，凍結部位に一致して大型の円形膨隆の構造物が複数みられた。膨隆内部には変性細胞群が存在した。化合物Ａガラクトース群でも膨隆構造物は時々見られたが、その大きさは小さかった。また、伸展標本でも角膜中央部に無数の核が密集している部位が見られた。

【００１３】凍結破壊後７日：正常対照群、化合物Ａガラクトース群でこの時期に重層化した部位が見られることはなく，完全に偏平化し正常化していた。ガラクトース単独群はこの時期でも半数以上の例で膨隆構造物は残存していた。５日目に見られた像に比べると重層の高さは減じ，内皮細胞も円形というより細長い細胞質のもので構成されていた。伸展標本像でも広範囲にわたり核の密集・重層部位が見られた。

【００１４】薬効薬理試験例２

薬効薬理試験例１の結果に基づき、本発明の明確な有用性を観察した。実験の方法は、実施例１に準じて実施し、（１）正常対照群、（２）ガラクトース単独群、（３）化合物Ａガラクトース群の凍結破壊後５日の角膜＊

＊を摘出した。ラットの左目の角膜を所定の方法でパラフィン包埋し、薄切後、ヘマトキシリン・エオジン染色を施し、光顕観察を行った。

【００１５】結果：

光顕観察

凍結部位の角膜内皮細胞の重層部位および隆起構造物は角膜内皮細胞障害の修復過程とされ、凍結破壊後５日の正常対照群では２５％の眼球に認められた。一方、ガラクトース単独群では１００％の全ての眼球に認められ、その差は統計学的に有意（Ｐ＜0.05）であり、角膜内皮細胞障害の修復が遅延していた。これに対し化合物Ａガラクトース群では、角膜内皮細胞の重層部位および隆起構造物は２２％の眼球に認められ、ガラクトース単独群に比べて統計学的に有意（Ｐ＜0.01）に正常化していた。化合物Ａの投与は、本モデルの角膜内皮細胞障害修復遅延を改善せしめることが統計学的にも明かになった。

【００１６】試験例２の結果（表１）

ガラクトース血症ラットの凍結破壊角膜内皮細胞の修復遅延に対する効果

［凍結破壊後５日の観察結果］

【００１７】

【表１】

処置	観察角膜数	障害修復遅延角膜数	（％）
（１）正常対照群	8	2	（２５）
（２）ガラクトース単独群	8	8	（１００）
（３）化合物Ａガラクトース群	9	2	（２２）

【００１８】以上のように糖尿病の最も簡便な動物モデルであるガラクトース血症ラットの角膜内皮細胞障害修復遅延に対し化合物Ａ投与は改善せしめ、臨床的にも糖尿病性角膜症を治療することが強く示唆された。

【００１９】製剤例等

化合物Ａ；(2S,4S)-6-フルオロ-2',5'- ジオキソスピロ［クロマン-4,4'-イミダゾリン］-2- カルボキサミド

【００２０】製剤例１

処方Ａ

１００ml中

化合物Ａ	０．１０ｇ
リン酸一水素ナトリウム	０．７６ｇ
リン酸二水素ナトリウム	０．１６ｇ
塩化ナトリウム	０．４２ｇ
塩化ベンザルコニウム	０．０１ｇ
滅菌精製水	適　量

【００２１】製法

滅菌精製水80mlにリン酸二水素ナトリウム、リン酸一水素ナトリウム、塩化ベンザルコニウムを加えて溶解した後、化合物Ａを加える。化合物Ａを溶解させた後、滅菌精製水を加えて全量を100ml とし、点眼剤に供する。

【００２２】処方Ｂ

１００ml中

化合物Ａ	０．１０ｇ
リン酸一水素ナトリウム	０．７６ｇ
リン酸二水素ナトリウム	０．１６ｇ
塩化ナトリウム	０．４０ｇ
塩化ベンザルコニウム	０．０１ｇ
ショ糖	０．０５ｇ
滅菌精製水	適　量

【００２３】製法

処方Ａと同様の方法で、点眼剤を製した。

【００２４】製剤例２

下記の表２に示される電荷調整剤0.4gと、精製卵黄レシチン1.6ｇ と、下記の表３に示される油性成分8.0gとをクロロホルム／メタノール（5/1,V/V ）混液50ml中で混合溶解した後、化合物Ａを0.1 ～1.0gを加え、溶媒を完全に除去する。これに滅菌精製水90g を添加し、マイクロフルイタイザーにより高圧（1500Kg/cm ² ）乳化し、10%(W/W)脂肪乳剤とする。

【００２５】処方

１００ml中

脂肪乳剤	５０．０ｇ
リン酸一水素ナトリウム	０．７６ｇ
リン酸二水素ナトリウム	０．１６ｇ
塩化ナトリウム	０．４０ｇ

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塩化ベンザルコニウム　　０．０１ｇ
ショ糖　　０．０５ｇ
滅菌精製水　　適　量

【００２６】製法
処方Ａと同様の方法で、点眼剤を製した。
【００２７】
【表２】

電　荷　調　整　剤
ジミリストイルホスファチジルグリセロール
ジミリストイルホスファチジン酸
ホスファチジルイノシトール
ホスファチジルセリン
オレイン酸
カプリン酸ナトリウム

【００２８】
【表３】

油　性　成　分
大　豆　油
中鎖脂肪酸トリグリセリド
酢酸トコフェロール
スクワラン

【００２９】製剤例３
処方

化合物Ａ	2㎎
ショ糖	２５㎎
結晶セルロース	３０㎎
乳糖	適　量
	１８０㎎

【００３０】製法

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化合物Ａとショ糖をエタノール／水（１／１，Ｗ／Ｗ）で練合し、乾燥後、結晶セルロース、乳糖を添加し、通常製剤に供される滑沢剤を加え、常法により錠剤、カプセル剤、顆粒剤等の経口製剤とする。
【００３１】製剤例４
処方

化合物Ａ	1㎎
ショ糖	１０㎎
結晶セルロース	３０㎎
乳糖	適　量
	１８０㎎

【００３２】製法
製剤例３と同様の方法で経口製剤を製した。
【００３３】
【発明の効果】糖尿病角膜症はその発生機序は未だ明らかではなく有効な治療薬も見出だされていないが、角膜上皮、知覚（シュワン細胞）および内皮細胞に種々の異常が認められる疾患であり、角膜の崩壊が重篤な場合，水泡性角膜症が発生し視機能を著しく障害する等しばしば難治性である。本発明は(2Ｓ,4Ｓ)-6-フルオロ-2',5'-ジオキソスピロ［クロマン-4,4'-イミダゾリン］-2-カルボキサミドを有効成分とする糖尿病性角膜症治療剤であり、殊に経口、点眼剤形態を有し、糖尿病性角膜上皮症、糖尿病性角膜知覚低下、糖尿病性角膜内皮症に効果を有する。

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